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Consequences of *Clostridium difficile* infection: understanding the healthcare burden

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Abstract

Clostridium difficile is the leading cause of infectious nosocomial diarrhoea in developed countries, with a measured incidence of approximately five episodes per 10 000 days of hospital stay in Europe. Accurate diagnosis of *C. difficile* infection (CDI) is a prerequisite for obtaining reliable epidemiological data, but in many European countries diagnosis is probably suboptimal. A significant percentage of CDI cases are missed because clinicians often fail to request tests for *C. difficile* toxins in cases of unexplained diarrhoea. In addition, some laboratories continue to use tests of low sensitivity or apply them inappropriately. In one study in Spain, failure to request CDI testing in more than two-thirds of patients with unexplained diarrhoea led to significant underdiagnosis of cases. A recent pan-European survey revealed huge discrepancies in the rate of CDI testing across Europe, which suggests that epidemiological reports underestimate the true incidence of CDI in many parts of Europe. This is important because, as this review of the clinical and economic burden of CDI illustrates, infection with *C. difficile* imposes a significant burden not only on patients, owing to increased morbidity and mortality, but also on healthcare systems and society in general. On the basis of current incidence rates, annual costs for management of CDI amount to approximately $800 million in the USA and €3000 million in Europe. Moreover, estimates suggest that costs associated with recurrent CDI can exceed those of primary CDI. Measures to more effectively prevent CDI and reduce CDI recurrence rates may help to reduce this burden.

Keywords: Burden, *Clostridium difficile*, *Clostridium difficile* infection, cost, incidence

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Introduction

Clostridium difficile is a Gram-positive, spore-forming, anaerobic bacillus and an important enteropathogen [1]. Responsible for both hospital-acquired and community-acquired diarrhoea, *C. difficile* is now recognized as the leading cause of infectious nosocomial diarrhoea among adults in industrialized countries [2], as well as being responsible for outbreaks of infectious diarrhoea in hospitals all over the world [3]. Colonization of the gastrointestinal tract occurs via the faecal–oral route following environmental exposure to *C. difficile* spores or from contact with an infected person or healthcare worker, who acts as a vector. Infection is facilitated by treatment with antibiotics, and especially broad-spectrum agents, which disturb the normal colonic microbiota, allowing toxigenic strains of *C. difficile* to flourish in the colon [4]. If patients are unable to mount a protective antibody response, infection can lead to overt clinical symptoms, which range from mild diarrhoea to pseudomembranous colitis and toxic megacolon at the severe end of the disease spectrum [5].

Once regarded as a cause of mildly troublesome antibiotic-associated diarrhoea in elderly hospitalized patients, *C. difficile* is increasingly being seen as a major public health problem in patients of all ages, hospitalized or living in the community, and with or without prior antibiotic treatment. In some hospitals,

the incidence of *C. difficile* infection (CDI) now exceeds that of methicillin-resistant *Staphylococcus aureus* [6].

Increased awareness of CDI, which has extended beyond the confines of the medical literature to include the mainstream media in some European countries, has arisen for several reasons. These include a marked increase in infection rates in younger populations [4], increasing severity of disease accompanied by increases in morbidity and mortality [7,8], and infection in patients who would not previously have been considered to be at risk [5]. In light of the recent epidemiological changes in CDI, this review will look at the clinical and economic impact of CDI on healthcare systems, focusing in particular on the burden caused by recurrent disease.

The Changing Epidemiology of CDI in Europe

Evidence for a change in the epidemiology of CDI first emerged in the USA and Canada, where rates of CDI were seen to increase markedly between 2000 and 2006 [9,10]. Data on discharge diagnosis rates in US hospitals showed that rates of CDI more than doubled, from <150 000 cases in 2001 to >300 000 in 2005 (http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf). This change in incidence marked the start of what has become a continuous rise in rates of CDI, not only in North America but also in Europe [11,12].

Historically, rates of CDI in Europe have been broadly similar to those reported in the USA, although surveillance for CDI has been more variable, reflecting differences in reporting regulations across Europe. For example, Spain does not require hospitals to report cases of CDI to the government, whereas the UK has very strict regulations requiring all cases to be reported [12]. To address deficiencies in CDI reporting across Europe, a pan-European hospital-based survey of CDI was carried out in November 2008 to obtain a more complete overview of CDI in Europe and to build capacity for improved diagnosis and ongoing surveillance [13]. The survey, which covered up to six hospitals in each of the 34 countries surveyed and included data on 395 *C. difficile* isolates, showed that CDI remains a predominantly nosocomial infection in Europe, with 80% of cases being acquired in hospitalized patients as compared with 14% in the community, and 6% being of indeterminate origin [13]. The incidence of CDI varied widely across Europe (as did rates of testing for CDI), with a mean incidence of nosocomial cases of 4.1 cases per 10 000 patient-days (range: 0.0–36.3). The measured incidence of CDI was relatively low in Spain, France, and Italy, but very much higher in Scandinavia, Ireland, and the UK [13] (Fig. 1). In the past decade, the hypervirulent 027 strain of *C. difficile* (or North American pulsed-field gel electrophoresis type 1 or restriction endonuclease analysis group BI, as it is more usually referred to in North America) has been identified as a key driver of the rapid increase in new cases of CDI in North America [8,14]. However, the pan-European survey revealed that the overall prevalence of ribotype 027 in Europe is at present relatively low, at *c.* 5% [13]. This suggests that strains other than ribotype 027 may have a more prominent role in driving increased rates of CDI in Europe. Among the European countries surveyed, ribotype 078, which is known to produce disease of similar severity to that caused by ribotype 027, occurred with a frequency of 8%. Other strains known to be associated with more severe CDI include ribotype 018, which occurred with an approximate overall frequency of 6% and accounted for 80% of all *C. difficile* strains in Italy, ribotype 015 (frequency of 3%), and ribotype 056 (frequency of 2%) [13]. The pan-European survey confirmed the significance of older age (≥65 years), severe comorbidity and prior antibiotic therapy as risk factors for CDI, with age ≥65 years, severe pulmonary comorbidity, previous fluoroquinolone use and infection with ribotypes 018 and 056 also being associated with worse outcomes [13].

Accurate diagnosis of CDI is a prerequisite for obtaining reliable epidemiological data on incidence and prevalence

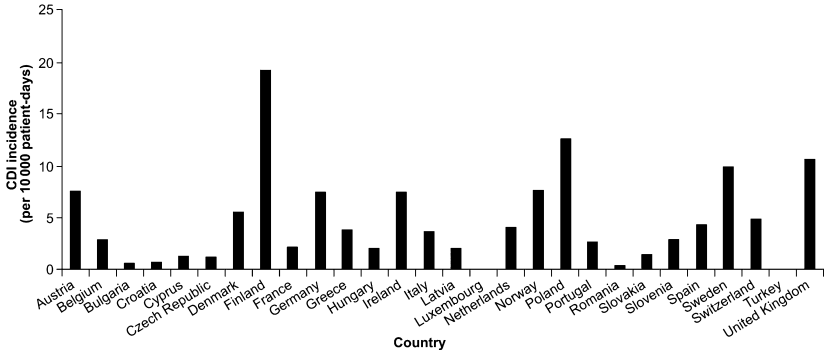

FIG. 1. The measured incidence of *Clostridium difficile* infection (CDI) across Europe in 2008 (adapted from Bauer *et al.* [13]).

rates, and yet, as a comprehensive survey of diagnostic protocols across Europe suggests, testing for CDI is suboptimal in many countries [15]. Recovering *C. difficile* from culture enhances the potential for diagnosis by permitting performance of a 'second-look' test for CDI [5]. A significant percentage of CDI cases are missed today because clinicians often fail to request tests for *C. difficile* toxins in cases of unexplained diarrhoea, and some laboratories use diagnostic tests with low sensitivity or that are not applied appropriately. A recently completed diagnostic study, in which confirmatory cultures were performed in our laboratory in Spain on diarrhoeal samples obtained on a single day from 118 Spanish laboratories covering 75.4% of the Spanish population, suggests that this is indeed the case [16]. Culture was performed on 807 diarrhoeal samples from 730 patients aged $\geq$2 years. The results showed that 63 (7.8%) were culture-positive for *C. difficile*, with 45 (5.6%) containing toxigenic strains [16]. However, the study revealed that more than two-thirds of cases went undiagnosed at the original hospital, mainly because there had been no request for CDI testing by the clinicians, and 19% had been misdiagnosed at the original hospital because the tests used in the laboratories were insufficiently sensitive. Had these specimens not been subjected to repeat testing for CDI at a central laboratory, rates of CDI would have been significantly lower than the incidence of 3.8 cases of CDI per 10 000 patient-days based on the culture results [16].

Although failure to request testing undoubtedly accounts for most under-reporting of CDI in Europe, the choice of diagnostic method may also play a part. For many years, standalone enzyme immunoassays for toxin detection have been used for CDI detection by most laboratories in Europe [15], and this probably reflects current practice. However, as two recent reviews have highlighted, these tests lack sensitivity when used as the sole diagnostic test for CDI [17,18]. Moreover, lack of confidence in such tests has led clinicians to submit multiple samples from the same patient for repeat testing, but, as the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) diagnostic guidelines stress, such an approach does not increase the rate of CDI detection in an endemic setting [1]. CDI detection rates can be improved significantly with the use of nucleic acid amplification tests for the detection of genes that encode *C. difficile* toxins [17,18], especially when restricted to patients with diarrhoea [17]. The wider adoption of such tests, several of which are now commercially available, should, in the longer term, help to address current deficiencies in the laboratory diagnosis of CDI and lead to better epidemiological reporting in the future.

Cases of CDI may also be missed because they occur following a patient's discharge from hospital even though the patient acquired *C. difficile* while in hospital. Data from a retrospective cohort study carried out in the USA show how inclusion of post-discharge CDI events can substantially alter hospital-specific CDI incidence rates (Fig. 2) [19]. Between 2000 and 2007, the hospital-onset CDI incidence increased from 15 per 10 000 admissions to 22 per 10 000 admissions, reflecting the rising incidence of CDI among hospitalized patients. When post-discharge CDI events were included in these figures, the incidence doubled from 29 per 10 000 in 2000 to 52 per 10 000 in 2007 [19]. Failure to include post-discharge CDI cases can lead to further under-reporting of CDI and inaccurate incidence rates. It is widely assumed that, within hospitals, infected patients are the primary source of onward transmission of *C. difficile* to other susceptible patients. However, a recent study in which molecular typing was used to match cases of nosocomially acquired CDI in >14 000 patients with diarrhoea, 1282 of whom had CDI, showed that, overall, no more than one-quarter of cases could be linked to an inpatient source [20]. This suggests that we need to be alert to sources of *C. difficile* contamination other than ward-based patient contact to understand the transmission of nosocomially acquired CDI.

CDI is still predominantly a healthcare-associated (nosocomial) infection; however, when appropriately searched for, it is also a cause of community-acquired diarrhoea [21–25]. Determining the precise origin of CDI can be difficult, but classification systems have been developed that distinguish between community-associated CDI and infections that originate in healthcare facilities where skilled nursing care is provided, such as hospitals and nursing homes [26]. A commonly used definition of community-associated CDI is that of symptom onset in the community or within 48 h of

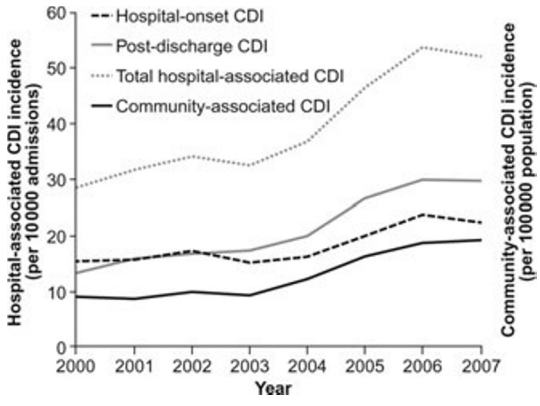

FIG. 2. The impact of post-discharge cases of *Clostridium difficile* infection (CDI) on the measured incidence over the period 2000–2007 (adapted from Murphy *et al.* [19]). Reprinted from Infect Control Hosp Epidemiol, Murphy CR, Avery TR, Dubberke ER *et al*, with permission from University of Chicago Press © 2011 by The Society for Healthcare Epidemiology of America. All rights reserved. 0899-823X/2012/3301-0005$15.00. DOI: 10.1086/663209.

admission to a healthcare facility, provided that symptom onset occurred >12 weeks after the last discharge from a healthcare facility [26]. By contrast, healthcare-associated CDI is defined as symptom onset occurring >48 h after admission to a healthcare facility [26].

Measured CDI incidence varies markedly across Europe, and may be influenced by high rates of testing in some countries. For example, the pan-European survey revealed marked differences in the clinical suspicion of CDI, as shown by the fact that the frequency of testing for infection varied by more than 47 times between countries (as expressed by the number of patients tested per 10 000 patient-days) [13]. Greater clinical suspicion of CDI in any patient presenting with unexplained diarrhoea together with greater awareness of post-discharge CDI and improved diagnosis will help us to build a more reliable picture of the true number of cases of CDI that occur annually in each European country.

The Clinical Burden of CDI

CDI imposes a considerable burden on patients from increased morbidity and mortality, as well as imposing a significant burden on the healthcare systems of developed countries. Patients experience considerable morbidity from the debilitating and profuse diarrhoea that is the hallmark of CDI. Other debilitating symptoms of mild to moderate disease can include fever and abdominal distension [5,27]. Where severe CDI progresses, then inflammatory lesions, the formation of pseudomembranes in the colon, or the development of paralytic ileus, toxic megacolon and fulminant colitis may occur [5,27]. Other complications of fulminant colitis include perforation of the bowel, sepsis, and shock [27].

Within the population of patients at increased risk of developing CDI, the clinical burden falls disproportionately not just on the elderly, who are most at risk of acquiring *C. difficile* [5], but also on those who have inflammatory bowel disease (IBD) concurrent with CDI [28], those who are seropositive for human immunodeficiency virus (HIV) infection [29], and those who undergo organ transplantation, particularly those with hypogammaglobulinaemia [30].

Patients with IBD are particularly susceptible to infection with *C. difficile*, the presence of which may be masked by the fact that diarrhoea is a common symptom of both Crohn's disease and ulcerative colitis. The outcome in patients with IBD can be severely compromised by CDI. A retrospective cohort study of almost 250 000 patients admitted to hospitals in England for IBD over a 6-year period showed that, among the 2402 patients who had IBD and concurrent CDI, death rates at 1 year were higher (33.1 vs. 6.7%, respectively) and inpatient stays longer (26 vs. 5 days, respectively) than for patients with IBD alone, and IBD patients with CDI were also twice as likely to undergo bowel surgery, including emergency colectomy [28]. Other groups of patients with compromised immune systems include HIV-seropositive patients and transplant recipients [29,30]. A recent systematic review of CDI in HIV-seropositive patients and transplant recipients suggests that acquisition of CDI is associated with a poorer prognosis in these patients than in immunocompetent individuals [29]. CDI, which caused diarrhoea in 43% of hospitalized HIV patients, and has been identified as the most common bacterial cause of HIV-related diarrhoea in other studies [31] and in up to 31% of transplant recipients, is itself debilitating. It exacerbates the state of immunosuppression by compromising nutrition and other factors that influence immune function. By prolonging hospitalization and the need for intravenous rehydration, CDI also increases the risk of hospital-acquired infection, including re-infection with *C. difficile*. This, in turn, will drive morbidity and mortality, particularly in the more severe cases, as highlighted in a recent review by Collini *et al.* [29].

Infection with toxigenic strains of *C. difficile* is a potentially life-threatening condition, especially among the small but increasing number of patients who develop fulminant colitis [32,33]; nonetheless, CDI can still cause death in patients with less severe disease [34]. Data from the pan-European survey showed that the overall mortality rate was 22%, with CDI being directly responsible for *c.* 2% of all deaths and a contributor to death in a further 7% of cases [13]. These rates are much lower than those reported for the UK, where CDI-attributable mortality rates have exceeded 20% for several years (http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-clostridium-difficile/2009/deaths-involving-mrsa–england-and-wales–2009.pdf). Although CDI-attributable mortality rates have historically been <2% in North America, rates have increased in the past decade. Recent data from three Canadian hospitals, in which death within 30 days of infection was used as a measure for CDI-attributable mortality, revealed a mortality rate of 37% [35]. It is suggested that this measure provides a more accurate estimate than cause of death on a death certificate. Conceivably, studies using data from death certificates may underestimate the mortality attributable to CDI, and some rates may actually be higher than those given in the literature.

The Burden of CDI Recurrence

Most patients with an initial episode of CDI will respond to treatment with either oral metronidazole or vancomycin. However, many patients will experience a recurrence of

diarrhoea within days to weeks of stopping treatment for the first attack [7,36,37]. Recurrence can arise either from a relapse of the original infection or following re-infection with a new strain of *C. difficile* from an exogenous source. Current treatment guidelines, including those from the ESCMID, argue that it is impossible in daily clinical practice to distinguish between relapse and re-infection, and 'recurrence' is therefore used as a generic term for both [27,38]. However, in the guidelines of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America, it is suggested that infection occurring after symptom resolution within 8 weeks of a previous infection is more likely to be a relapse and to result from treatment failure, whereas infection occurring >8 weeks after a previous infection (no positive result within the previous 8 weeks) is more likely to result from re-infection [38].

Older age, a compromised immune system, diabetes mellitus, recent surgery (within a month), exposure to more than three antibiotics, long hospital stays and continued use of previous antibiotics are among the risk factors for recurrent CDI [9,39–42]. Other factors associated with recurrent CDI include prolonged disturbance of the normal colonic microflora, persistence of spores in the gut, and a failure to mount an effective immune response to *C. difficile* and its toxins [41,43,44]. In the pan-European survey described earlier, 18% of patients experienced recurrent CDI [13], and other studies have reported rates of up to 25% within 30 days following treatment with either metronidazole or vancomycin [7,36,45] (Fig. 3). Even higher rates of 47% following treatment with metronidazole have been documented in one Canadian study [9]. Patients who have experienced one recurrent episode of CDI are at significantly increased risk of further recurrences [37,46]. In one report, 45% of patients (n = 163) experienced a second recurrence of CDI [46], and in a study in which patients had had an average of 3.2 prior episodes of CDI, the recurrence rate was 65% [37] (Fig. 3).

The ESCMID has identified recurrent CDI as the major shortcoming of current treatments [27], and it is arguably the most common complication of treatment with metronidazole or vancomycin [5,37,47,48]. Patients who experience recurrent CDI have to endure prolonged symptoms associated with the disease [47]. Recurrent CDI leads to repeated courses of antibiotic treatment and the risk of adverse events as well as re-hospitalization. Like patients with an acute episode of CDI, patients with recurrent CDI serve as a reservoir of infection that can lead to secondary infection in other vulnerable patients [43].

The Economic Burden of CDI

Given that CDI usually develops in patients who are already hospitalized for treatment of an underlying condition, the extra costs associated with the management of CDI could be expected to be trivial. However, as health economic studies have demonstrated, the costs associated with each hospitalized case of CDI are by no means trivial [49,50]. Patients colonized with *C. difficile* who develop CDI require isolation, supportive therapy for underlying diseases, and specific antibiotic therapy to eliminate *C. difficile* from the bowel. As compared with the costs of such measures, antibiotic therapy for CDI represents only a small part of the cost burden, i.e. *c.* 1% of the total costs of care [51]. Understandably, drug acquisition costs in general will vary, depending on local protocols and the country in which one operates. The availability of branded vancomycin capsules for oral administration and new antibiotics such as fidaxomicin will be relevant to clinicians managing patients with CDI. However, acquisition costs for treatments should be considered in the context of the wider costs of managing CDI. In the small percentage of patients who develop serious complications, significant additional costs will also arise from the need for surgery and postoperative care.

On average, patients with CDI spend an extra 1–3 weeks in hospital as compared with non-infected patients. Increased duration of hospitalization is a major, if not the major,

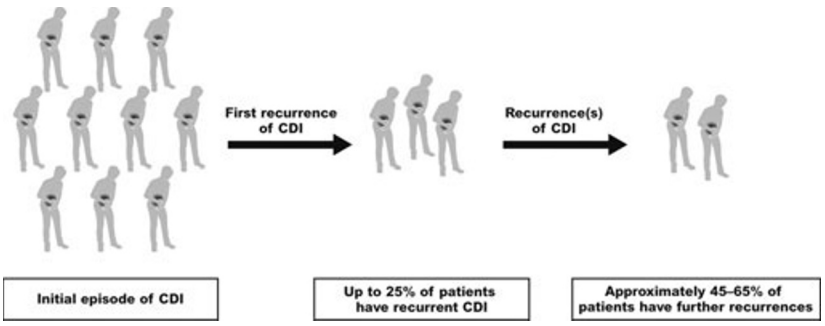

FIG. 3. The frequency of *Clostridium difficile* infection (CDI) recurrence [7,36,37,45,46].

contributor to increased costs [49]. Additional costs accrue from the need for rigorous hygiene in patient care, environmental decontamination, and, when outbreaks occur, cohort isolation and ward closure [11]. Data from a matched case–control study illustrate the excess costs associated with the management of CDI. The average total cost of care for each CDI patient was €33 840, which was greater than the €18 981 cost of care for the control cohort. When the additional cost of treating CDI was analysed on a per patient episode basis, this ranged from an extra €4067 to an extra €9276 [50]. Consistent with other studies, CDI patients in this study spent significantly longer in hospital than matched non-infected controls (a median of 7 days longer; p 0.006). However, the costs per patient-day were not significantly different between those with CDI and the non-infected controls (€1110 vs. €1034, respectively) [50]. These findings are supported by data from a systematic review of the healthcare costs associated with caring for patients with primary and recurrent CDI [52]. Based on the results from 13 studies that met inclusion criteria, the analysis showed that total costs in 2008 US dollars for treating primary CDI ranged from $9822 to $13 854, as compared with $6950 to $9008 for controls. Costs escalated in patients with significant comorbidity, such as IBD patients, where costs were $22 873 per case as compared with $15 762 for non-infected IBD patients [52]. As expected, the attributable or incremental costs associated with CDI (Table 1) were largely attributable to increased duration of hospitalization [52]. With the use of data derived from this systematic review and estimated annual cases of CDI in the USA, attributable healthcare costs of CDI in the USA were estimated to be in the range of $433 million to $797 million per year [52]. These estimates are consistent with figures of $496 million to $797 million per year obtained from an economic model that was designed to simulate the costs associated with CDI from the perspective of the hospital, third-party payer, and society in general (Table 2) [53].

Separately, the high rates of recurrent CDI associated with currently available antibiotics not only increase morbidity, with some patients experiencing repeated recurrences over months and years, leading to exhaustion and protein-losing enteropathy [27], but also add to the burden of costs of care. Additional costs arise from extended re-hospitalization, laboratory tests to confirm a recurrent infection, and the cost of additional and often extended antibiotic treatment. Data from the systematic review showed that total costs for recurrent CDI were approximately three-fold higher than for a primary episode of CDI [52].

As these data demonstrate, the economic consequences of CDI are substantial, and often exceed the costs of treating other hospital-acquired infections, such as viral gastroenteritis [53]. In Europe alone, estimates suggest that the potential costs associated with the management of CDI are in the region of €3000 million [11]. This figure is likely to rise in line with an ageing population: by 2050, >134 million Europeans will be aged ≥65 years [11]—the segment of the population most at risk of contracting CDI.

As this review has illustrated, CDI imposes a considerable burden on patients from increased morbidity and mortality, as well as imposing a significant burden on the healthcare systems of developed countries. From a European perspective, the findings presented here are consistent with those from a systematic review recently published by Wiegand *et al.* [54]. Using country-specific estimates and weighting by sample size, the authors showed that the 30-day mortality from CDI ranged from 2.8% to 29.8% across Europe, with CDI patients spending anywhere between 16 and 37 extra days in hospital. More effective measures to prevent primary cases of CDI and

TABLE 1. Attributable or incremental costs associated with the management of *Clostridium difficile* infection (CDI) in hospitalized patients [52]

Study description	Location	Year	Attributable or incremental costs associated with CDI in 2008 US dollars
Retrospective chart review (n = 155)	USA	1991	9099
Prospective case–control study (n = 142)	UK	1996	9277
Prospective cohort study in recurrent CDI (n = 209)	USA	1999	2626
Retrospective study (n = 87)	Ireland	2000	6890
Prospective study (n = 271)	USA	2002	3669
Laboratory-based prevalence study (n = 2062)	Canada	2002	12 099
Retrospective cohort study (n = 3692)	USA	2007	13 675
Retrospective study (n = 8133)	USA	2007	77 483
Retrospective cohort study (n = 1835)	USA	2007	5325–27 290
Retrospective cohort study (n = 24 691)	USA	2008	2454–5042
Retrospective study in IBD patients (n = 44 400)	USA	2008	11 000

IBD, inflammatory bowel disease.
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TABLE 2. Costs associated with *Clostridium difficile* infection (CDI) from the hospital, third-party payer and societal perspective in the USA [53]

Median cost per case of CDI (in 2010 US dollars)	
Hospital perspective	9179–11 456
Third-party payer perspective	8932–11 679
Societal perspective	13 310–16 464
Annual burden of CDI (in 2010 US dollars)	
Hospital perspective	496 million
Third-party payer perspective	547 million
Societal perspective	796 million

reduce the frequency of CDI recurrence would represent an important advance in reducing the costs associated with this pernicious nosocomial pathogen.

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